Herd Immunity: A Cautionary Note

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Summary

When influenza epidemics and pandemics end, a key reason is that herd immunity prevents further infection in the population. The immune population contributing to herd immunity is comprised of those who have survived the infection and those who have been successfully vaccinated. Vaccination is not a major contributor in poor nations as most people are not vaccinated; and in developed nations, vaccinations against influenza are often less than 50% effective.

A few years back, I gave a lecture on business issues surrounding new antibiotic and antiviral development. Over 50% of my students were PhDs looking at the biotechnology and pharmaceutical industries as career prospects, as academic positions were dwindling. Since we were talking about infectious disease, the concept of herd immunity came up more than once. Herd immunity seemed to be stated as an absolute barrier against further infection, which spurred me to better understand the phenomenon. One of my new understandings was that more virulent influenza virus strains created in the lab from recent epidemic strains could break through the herd-immunity barrier and seed a new epidemic.

If enhanced virulence is accompanied by enhanced airborne or contact transmission, then the basic reproductive number, R_0, could increase, creating a higher herd-immunity threshold. A release into the community could cause the number of people infected to increase substantially until the new threshold is reached. This is the key observation of the simple analysis here.

The 2009 influenza pandemic (pdm09 H1N1) is used as an illustration. This recent pandemic infected 20-27% of the world's population[1] before it ended. The acquired herd immunity to the virus plus vaccination may not provide protection against new infections from an accidental release into the community of a lab-enhanced more virulent and transmissible strain of pdm09 H1N1. Nearly a billion new world-wide infections with potentially higher case-fatality rates could result since the new strains are more virulent. This is a highly worrisome, large number and should be a concern to all of us.

A legitimate research goal during the active pandemic was finding what could make pdm09 H1N1 strains more virulent. Creating more virulent strains in the laboratory is one way of studying that. Using the single search term "2009 H1N1 pandemic influenza mutagenesis virulence," a Pub Med search identified sixteen publications of lab-created pdm09 H1NI virus strains with enhanced virulence, some with likely

enhanced transmission. Given the rapidity that human influenza viruses can travel around the world infecting a significant percentage of the world's population, alternative methods that do not employ live virus[2] should have been employed.

Adding significantly to the concern, some of this research appears to be carried out at low BSL2 containment, where the probability of a laboratory release could be much greater than BSL3. BSL2 may have been deemed sufficient because of presumed herd immunity acquired from the 2009 pandemic. Low containment BSL2 research creating enhanced virus is not acceptable.

Herd-immunity threshold theory and reproductive numbers

The following argument based on simple mathematical analysis will make the point that the 2009 pandemic could have been re-seeded leading to a very large number of new infections. The analysis is based on the long-known theory of herd-immunity threshold[3].

The basic reproductive number, R_0, is the average number of people infected by a single infected person. The zero subscript indicates that this is the reproductive number at the beginning of a new epidemic.

Reproductive number decreases as the epidemic expands. This decreasing reproductive number is called the effective reproductive number, R_E. It decreases because an infected person encounters fewer susceptible people to infect as some of the people encountered will be immune from surviving infection or have been vaccinated.

As the fraction of immune people in the population, i, increases, the effective reproductive number is

$$R_E = (1-i)\, R_0 \qquad (1)$$

From equation (1) when i=0, $R_E = R_0$ as expected. Equation (1) also has the property that R_E decreases linearly as i increases; that is, an infected individual can only infect encountered susceptible people by subtracting out from R_0 the encountered immune people.

R_E eventually falls to $R_E<1$, where the infection will soon end because each infected individual can then infect less than one person on average, so the epidemic grinds to a halt in a short time. When $R_E>1$, the fraction immune will continue to increase as infections increase until $R_E=1$, the so-called "herd-immunity threshold."

The fraction immune in the population at the threshold is denoted by the letter H.

Setting $R_E=1$ and i=H, equation (1) becomes

$$1 = (1-H)\, R_0$$

which when solved for H yields

$$H = 1 - (1/R_0) \qquad (2)$$

This is the literature equation[4] relating the herd-immunity threshold to basic reproductive number. A key observation from equation (2) is that the threshold H increases as R_0 increases.

Calculation of herd-immunity thresholds and the size of a potential new pandemic

Since the 2009 H1N1 pandemic has long passed, the relevant fraction of the population immune today, PI, would be those immune after the 2009 pandemic. PI=H+V, where V is the fraction effectively vaccinated[5]. For poor nations, where there is little to no vaccination, PI=H. Unvaccinated nations is the example to be explored here.

For the pdm09 H1N1 pandemic virus, the median reproductive number was 1.46 with a range 1.30–1.70.[6] From equation (2) for R_0 = 1.46, the herd -immunity threshold, H, is reached when 32% of the population is immune.

For a lab-enhanced pdm09 H1N1 strain, the circumstantial evidence for a likely increase in airborne or contact transmission is increased viral titers in lung-derived cells *in vitro* or in lung cells in ferrets or mice, which could imply a significant increase in R_0. If a new strain with increased R_0 arises, the herd-immunity threshold rises. *Consequently, the number of people infected would rise until the new immune threshold is reached.*

There are a number of assumptions in the analysis, including the use of only the median R_0 value[7] and a homogeneous population. Additionally, laboratory evidence suggesting increased transmission cannot provide R_0 values, as R_0 cannot be determined in a laboratory setting with only a few animals. These are reasons why only an illustrative quantitative analysis is possible. Consequently, the following should be viewed only as a means to alert us to concerns over the pandemic risk of this research.

Assume a modest increase in R_0 from R_0=1.46 to R_0=1.8 for a post-pandemic lab release of a transmission-enhanced pdm09 H1N1 virus. From equation (2), the new herd-immunity threshold rises to H=0.44, increased from H=0.32.

Assume unvaccinated nations comprise about 80% of the world's population[8] or 0.8x7.6 billion=6 billion people. The number susceptible to infection would be (0.44-0.32) x 6 billion = 0.72 billion additional people could be infected until the new threshold is reached.

Since these lab-enhanced strains are more virulent than the wild-type strains, the case-fatality rate may increase as well. Potential new infections of 0.72 billion with higher case-fatality rate is highly worrisome and should be a grave concern for us all. Do not fall for the false promise of herd immunity.

For nations with high vaccination rates, herd immunity plus vaccination may or may not protect the population from significant further infection depending on the lab-enhanced virus R_0 value and vaccine effectiveness.

Even if all lab personnel were vaccinated, which is likely the case, release from a lab could occur from a laboratory-acquired infection if vaccination was not effective. For BSL2 labs, virus could be transported out of the lab into the community on the bodies and clothing of lab personnel. Ineffective vaccination is an Achilles heel as far as lab-releases are concerned.

Literature evidence for enhanced virulence and transmissibility of lab-created pdm09 H1N1

There are many published research studies that create in the lab pdm09 H1N1 strains with enhanced virulence. Table 1 lists publication titles, biosafety level, countries creating and conducting the research, along with an assessment of whether the lab-enhanced virulent strains are likely accompanied by

increased R_0 from increased airborne or contact transmission. Increased airborne or contact transmission appeared likely in eight of the sixteen studies and eleven of the sixteen studies appeared to be carried out at low BSL2 containment.

Tracking Number	Article Title	BSL Level	Countries of Research	Increased Airborne or contact transmission?
1	A PB1 T296R substitution enhance polymerase activity and confer a virulent phenotype to a 2009 pandemic H1N1 influenza virus in mice	BSL3	China	**Likely**, lung cells infected
2	Impact of the H275Y and I223V Mutations in the Neuraminidase of the 2009 Pandemic Influenza Virus In Vitro and Evaluating Experimental Reproducibility	unknown, (BSL2?)	Canada	**Possible**, study on Madin-Darby canine kidney (MDCK) cells cells only, no lung cell or animal experiments
3	The contribution of PA-X to the virulence of pandemic 2009 H1N1 and highly pathogenic H5N1 avian influenza viruses	BSL3	China, UK	**Likely**, viral replication in A549 lung cells increased
4	PB2-588I enhances 2009 H1N1 pandemic influenza virus virulence by increasing viral replication and exacerbating PB2 inhibition of beta interferon expression	unknown, (BSL2?)	China	**Likely,** Virus titer in lungs of mice was increased
5	Asparagine substitution at PB2 residue 701 enhances the replication, pathogenicity, and transmission of the 2009 pandemic H1N1 influenza A virus	BSL2	US	**Yes**, but only 3 ferrets used in WT experiments and 3 ferrets in mutant pdm09 H1N1 experiments
6	Substitutions T200A and E227A in the hemagglutinin of pandemic 2009 influenza A virus increase lethality but decrease transmission	unknown, (BSL2?)	US, Nertherlands	**No**, ferret transmission experiments were performed
7	Mutations in polymerase genes enhanced the virulence of 2009 pandemic H1N1 influenza virus in mice	unknown, (BSL2?)	China	**Likely**, virus titer in lungs of mice was increased
8	Impact of mutations at residue I223 of the neuraminidase protein on the resistance profile, replication level, and virulence of the 2009 pandemic influenza virus	unknown, (BSL2?)	Canada, UK	**Unlikely**, found no significant differences between WT and mutants
9	Synergistic adaptive mutations in the hemagglutinin and polymerase acidic protein lead to increased virulence of pandemic 2009 H1N1 influenza A virus in mice	unknown, (BSL2?)	Germany, US	**Likely**, increased virus titer observed in human lung epithelial cell line (A549)
10	The 2009 pandemic H1N1 D222G hemagglutinin mutation alters receptor specificity and increases virulence in mice but not in ferrets	unknown, (BSL2?)	Canada	**Likely**, contact transmissibility measured but levels compared to WT may be the same. Higher lung viral titers observed.
11	PA residues in the 2009 H1N1 pandemic influenza virus enhance avian influenza virus polymerase activity in mammalian cells	unknown, (BSL2?)	US	**Possible**, virus containing the 85I mutation grew faster in human A549 cells
12	Impact of amino acid mutations in PB2, PB1-F2, and NS1 on the replication and pathogenicity of pandemic (H1N1) 2009 influenza viruses	unknown, (BSL2?)	US, Japan	**Unlikely**, virus titers in respiratory organs were comparable to those of the wild-type virus
13	Virulence-associated substitution D222G in the hemagglutinin of 2009 pandemic influenza A(H1N1) virus affects receptor binding	unknown, (BSL2?)	Netherlands, US, UK	**Unlikely**, no enhanced transmissibility from the lab-created mutants compared to WT
14	D225G mutation in hemagglutinin of pandemic influenza H1N1 (2009) virus enhances virulence in mice	BSL3	China	**Likely**, higher viral titers in lung homogenates . No transmission experiments performed
15	Introduction of virulence markers in PB2 of pandemic swine-origin influenza virus does not result in enhanced virulence or transmission	BSL3+	Netherlands, US,	**Unlikely**, the impact of key known virulence markers in PB2 in the context of current S-OIVs was surprisingly small
16	Experimental adaptation of an influenza H5 HA confers respiratory droplet transmission to a reassortant H5 HA/H1N1 virus in ferrets	BSL3+	US, Japan	**Possible**, droplet transmission with H5 in (A/California/04/2009, CA04) background, but might not be more transmissible or virulent that WT

Table 1. Titles of publications of lab-enhanced pdm09 H1NI strains with increased virulence, biosafety level, location of the research, and an assessment of whether the research produced increased airborne or contact transmission strains. When biosafety level is reported as "unknown," it usually means that the research was carried out at BSL2.
Publication titles may be used to download the publications.

Comparison of pandemic risk for matH5N1 and pdm09 H1N1 with enhanced transmission

Controversy over lab-created pandemic risk arose in 2011 when Dutch researcher Ron Fouchier[9] and American virologist Yoshihiro Kawaoka[10] submitted manuscripts to Science and Nature where they described how to create strains of H5N1 avian influenza that were mammalian airborne transmissible

(matH5N1). Does the pandemic risk from the lab-enhanced pdm09 H1N1 virus strains discussed here rival that of the matH5N1?

Wild-type strains of pdm09 H1N1 had spread throughout the world. More virulent strains of this already airborne transmissible virus, could have greater but unknown reproductive numbers. For matH5N1, the virus is airborne transmissible between ferrets in the laboratory, so it is reasonable to assume the virus would be airborne transmissible in humans as well; however, there is no way of estimating reproductive numbers in human populations.

For pdm09 H1N1, the world case-fatality rate was a surprisingly low 0.001–0.011%,[11] from which 76,000 to 836,000 deaths can be calculated based on a world population of 7.6 billion. The case-fatality rate could increase substantially for more virulent lab-enhanced strains but cannot be estimated. For avian H5N1, the case-fatality rate is 60% for poultry workers and others directly infected by handling infected birds. The case-fatality rate in the human population for the matH5N1 virus cannot be estimated. It could be much lower than 60%, but could still cause fatalities in the millions with 1% case-fatality rate.

Both lab-enhanced pdm09 H1N1 and matH5N1 present a potential risk of significant population infection with high fatalities. Potential risk = (likelihood) x (consequences), so even if the likelihood of a release from a laboratory seeding a pandemic is small, the consequences are potentially high for both lab-created pdm09 H1N1 and matH5N1. Furthermore, since the benefits of the research are uncertain, there are good reasons for concern over conducting this research on live influenza viruses that could quickly spread throughout the world.

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[1] *One-fifth of the world had swine flu due to 2009 pandemic – WHO report*, https://www.rt.com/news/swine-flu-pandemic-who-815/

[2] For instance, see Lipsitch M, Galvani AP (2014) *Ethical Alternatives to Experiments with Novel Potential Pandemic Pathogens*. PLoS Med 11(5): e1001646. https://doi.org/10.1371/journal.pmed.1001646

[3] *''Herd Immunity'': A Rough Guide* (http://op12no2.me/stuff/rough.pdf

[4] *Ibid*

[5] An aside on vaccination against the pdm09 H1N1 virus: About 27% of the U.S. population was vaccinated against the pdm09 H1N1 virus (Effects of Vaccine Program against Pandemic Influenza A(H1N1) Virus, United States, 2009–2010, Table 1 (https://wwwnc.cdc.gov/eid/article/19/3/pdfs/12-0394.pdf)). For the pdm09 H1N1 virus, vaccine effectiveness varied depending on vaccine type and sub-population vaccinated. The overall effectiveness for the pandemic vaccines was 56% (doi:10.1371/journal.pone.0023085). Thus, the average percentage of the population immune post-pandemic from vacinationis 0.27x0.56=0.15 or 15%.

[6] Biggerstaff, *et al., Estimates of the reproduction number for seasonal, pandemic, and zoonotic influenza: a systematic review of the literature.* (https://bmcinfectdis.biomedcentral.com/articles/10.1186/1471-2334-14-480)

[7] *Ibid.* There is considerable variability in pdm09 H1N1 basic and effective reproductive numbers.

[8] https://en.wikipedia.org/wiki/List_of_continents_by_population

[9] S Herfst, *et al.*, *Airborne Transmission of Influenza A/H5N1 Virus Between Ferrets,* Science 22 Jun 2012: Vol. 336, Issue 6088, pp. 1534-1541, DOI: 10.1126/science.1213362 http://science.sciencemag.org/content/336/6088/1534.full

[10] M Imai, *et al.*, Experimental adaptation of an influenza H5 HA confers respiratory droplet transmission to a reassortant H5 HA/H1N1 virus in ferrets, Nature volume 486, pages 420–428 (21 June 2012) doi:10.1038/nature10831 http://www.nature.com/articles/nature10831

[11] Dawood, F. S., *et al.*, Estimated global mortality associated with the first 12 months of 2009 pandemic influenza A H1N1 virus circulation: a modelling study. Lancet Infect Dis. Volume 12, No. 9, p687–695, September 2012 https://www.thelancet.com/pdfs/journals/laninf/PIIS1473-3099(12)70121-4.pdf